

Bölüm 22

GABAPENTİNOİDLER

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GİRİŞ

Gabapentinoidler (pregabalin ve gabapentin) epilepsi ve ağrı tedavisinde yaygın olarak kullanılan ilaçlardır¹. Pregabalin ek olarak yaygın anksiyete bozukluklarında, diyabetik periferik nöropatide, postherpetik nöraljide ve fibromyaljide de kullanılmaktadır². Yakın zamanda Japonya'da periferik nöropatik ağrı için ruhsat almış bir başka gabapentinoid de mirogabalin'dir³. Bağımlılık potansiyellerinin göz ardı edilmesi ile birlikte, son yıllarda gabapentinoidlerin ruhsatlı ve ruhsatsız endikasyonlarında kullanımları giderek artmaktadır⁴. Bazı çalışmalar gabapentinoidlerin kötüye kullanım potansiyellerinin opioidler, alprazolam ve zolpidemle benzer olduğunu göstermektedir^{5,6}. Son yıllarda farmakovijilans veri tabanlarında gabapentinoid suistimali ile ilgili yan etki bildirimleri artmış olup^{7,8}, postmortem toksikoloji analizlerinde çoklu madde kullanımı ile oluşan aşırı doz ölümlerde gabapentinoidler daha fazla tespit edilmeye başlanmıştır⁴. Buna karşın gabapentinoid suistimali ile ilgili literatürde yer alan yayınların, gerçek popülasyondaki oranları yansıtmadığı görülmektedir. Gabapentinoidlerin kötüye kullanımları ile ilgili çalışmalarda prevelans oranları arasında büyük farklılıklar olduğu göze çarpmaktadır^{1,4,5}.

Gabapentinoid suistimali ile ilgili ele alınması gereken diğer konular arasında reçete edilmeden yasadışı olarak da kötüye kullanılabildikleri ve bu ilaçlara kolay ulaşabilen sağlık personeli arasında kötüye kullanım sıklıklarının daha fazla olabileceği de yer almaktadır. Bu bölümde son yıllarda kullanımlarının ve suistimal oranlarının arttığı bilinen gabapentinoidlerin etki mekanizmaları, ruhsatlı ve ruhsatsız endikasyonlarında kullanımları ve bağımlılık potansiyelleri hakkında öz bilgi verilmesi amaçlanmıştır.

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Kanser ağrıları dışındaki kronik ağrı hastalarında opioid kullanımını azaltma stratejileri, klinisyenleri opioid olmayan analjezik ilaç alternatiflerine yönlendirmiş ve ilk sırayı gabapentinoidler almıştır. Ancak, opioid kullanmaya devam eden kronik ağrı hastalarında gabapentinoidlerin de tedaviye eklenmesi opioid alımı ile oluşan öforinin gabapentinoidler ile pekiştirilmesi ile sonuçlanabilir.

Kronik ağrıların tedavisi özellikle de birinci basamak sağlık kurumlarında oldukça zordur. Kronik ağrısı olan hastaların çoğu bilişsel davranış tedavileri, fizyoterapi gibi ilaç tedavisi dışındaki diğer tedavi alternatiflerine ulaşamamakta ya da tercih etmemektedir. Gabapentinoidler ruhsatsız endikasyonlarında reçete edilirken, ilaçların yan etkileri ve bağımlılığa neden olabilecekleri değerlendirilerek hasta tedaviden yarar görmezse gabapentinoid tedavisi kesilmelidir. Gabapentinoidlerin kronik ağrı tedavisinde opioid analjeziklerden daha iyi bir alternatif olarak kullanımları teşvik edilse de gabapentinoidlerin de yan etkileri olduğu, suistimal edilebildikleri, bağımlılık oluşturabildikleri ve özellikle opioid bağımlılarında pekiştiri oluşturmak amacıyla suistimal edilerek opioid aşırı doz alımlarına bağlı ölümleri kolaylaştırabileceği unutulmamalıdır.

KAYNAKLAR

1. Hägg S, Jönsson AK, Ahlner J. Current Evidence on Abuse and Misuse of Gabapentinoids. *Drug Saf* 2020; 43(12):1235-1254. Doi: 10.1007/s40264-020-00985-6.
2. Calandre EP, Rico-Villademoros F, Slim M. Alpha(2)delta ligands, gabapentin, pregabalin and mirogabalin: a review of their clinical pharmacology and therapeutic use. *Expert Rev Neurother* 2016; 16(11):1263-1277. Doi: 10.1080/14737175.2016.1202764.
3. Deeks ED. Mirogabalin: First Global Approval. *Drugs* 2019; 79(4):463-468. Doi: 10.1007/s40265-019-01070-8.
4. Evoy KE, Covvey JR, Peckham AM, Reveles KR. Gabapentinoid misuse, abuse and non-prescribed obtainment in a United States general population sample. *Int J Clin Pharm* 2021. Doi: 10.1007/s11096-020-01217-8.
5. Peckham AM, Fairman KA, Sclar DA. Prevalence of Gabapentin Abuse: Comparison with Agents with Known Abuse Potential in a Commercially Insured US Population. *Clin Drug Investig* 2017; 37(8):763-773. Doi: 10.1007/s40261-017-0530-3.
6. Peckham AM, Evoy KE, Covvey JR, Ochs L, Fairman KA, Sclar DA. Predictors of Gabapentin Overuse With or Without Concomitant Opioids in a Commercially Insured U.S. Population. *Pharmacotherapy* 2018; 38(4):436-443. Doi: 10.1002/phar.2096.
7. Evoy KE, Covvey JR, Peckham AM, Ochs L, Hultgren KE. Reports of gabapentin and pregabalin abuse, misuse, dependence, or overdose: An analysis of the Food And Drug Administration Adverse Events Reporting System (FAERS). *Res Social Adm Pharm* 2019; 15(8):953-958. Doi: 10.1016/j.sapharm.2018.06.018.
8. Buttram ME, Kurtz SP, Dart RC, Margolin ZR. Law enforcement-derived data on gabapentin diversion and misuse, 2002-2015: diversion rates and qualitative research findings. *Pharmacoepidemiol Drug Saf* 2017; 26(9):1083-1086. Doi: 10.1002/pds.4230.
9. Johansen ME. Gabapentinoid Use in the United States 2002 Through 2015. *JAMA Intern Med* 2018; 178(2):292-294. Doi: 10.1001/jamainternmed.2017.7856.
10. Goodman CW, Brett AS. A Clinical Overview of Off-label Use of Gabapentinoid Drugs. *JAMA Intern Med* 2019; 179(5):695-701. Doi: 10.1001/jamainternmed.2019.0086.

11. Landefeld CS, Steinman MA. The Neurontin legacy--marketing through misinformation and manipulation. *N Engl J Med* 2009; 360(2):103-6. Doi: 10.1056/NEJMp0808659.
12. Steinman MA, Bero LA, Chren MM, Landefeld CS. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Ann Intern Med* 2006; 145(4):284-93. Doi: 10.7326/0003-4819-145-4-200608150-00008.
13. Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *N Engl J Med* 2009; 361(20):1963-71. Doi: 10.1056/NEJMs0906126.
14. Gorson KC, Schott C, Herman R, Ropper AH, Rand WM. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. *J Neurol Neurosurg Psychiatry* 1999; 66(2):251-2. Doi: 10.1136/jnnp.66.2.251.
15. Rauck R, Makumi CW, Schwartz S, Graff O, Meno-Tetang G, Bell CF, Kavanagh ST, McClung CL. A randomized, controlled trial of gabapentin enacarbil in subjects with neuropathic pain associated with diabetic peripheral neuropathy. *Pain Pract* 2013; 13(6):485-96. Doi: 10.1111/papr.12014.
16. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *Jama* 1998; 280(21):1831-6. Doi: 10.1001/jama.280.21.1831.
17. Sandercock D, Cramer M, Biton V, Cowles VE. A gastroretentive gabapentin formulation for the treatment of painful diabetic peripheral neuropathy: efficacy and tolerability in a double-blind, randomized, controlled clinical trial. *Diabetes Res Clin Pract* 2012; 97(3):438-45. Doi: 10.1016/j.diabres.2012.03.010.
18. Wiffen PJ, Derry S, Bell RE, Rice AS, Tölle TR, Phillips T, Moore RA. Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2017; 6(6):Cd007938. Doi: 10.1002/14651858.CD007938.pub4.
19. Mathieson S, Maher CG, McLachlan AJ, Latimer J, Koes BW, Hancock MJ, Harris I, Day RO, Billot L, Pik J, Jan S, Lin CC. Trial of Pregabalin for Acute and Chronic Sciatica. *N Engl J Med* 2017; 376(12):1111-1120. Doi: 10.1056/NEJMoa1614292.
20. Arnold LM, Goldenberg DL, Stanford SB, Lalonde JK, Sandhu HS, Keck PE, Jr., Welge JA, Bishop F, Stanford KE, Hess EV, Hudson JI. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum* 2007; 56(4):1336-44. Doi: 10.1002/art.22457.
21. Arnold LM, Russell IJ, Diri EW, Duan WR, Young JP, Jr., Sharma U, Martin SA, Barrett JA, Haig G. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *J Pain* 2008; 9(9):792-805. Doi: 10.1016/j.jpain.2008.03.013.
22. Dworkin RH, Barbano RL, Tyring SK, Betts RF, McDermott MP, Pennella-Vaughan J, Bennett GJ, Berber E, Gnann JW, Irvine C, Kamp C, Kiebertz K, Max MB, Schmader KE. A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. *Pain* 2009; 142(3):209-217. Doi: 10.1016/j.pain.2008.12.022.
23. Krceviski Skvarc N, Kamenik M. Effects of pregabalin on acute herpetic pain and postherpetic neuralgia incidence. *Wien Klin Wochenschr* 2010; 122 Suppl 2:49-53. Doi: 10.1007/s00508-010-1345-x.
24. Moore A, Derry S, Wiffen P. Gabapentin for Chronic Neuropathic Pain. *Jama* 2018; 319(8):818-819. Doi: 10.1001/jama.2017.21547.
25. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. *Jama* 2016; 315(15):1624-45. Doi: 10.1001/jama.2016.1464.
26. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iverson DJ, Perkins B, Russell JW, Zochodne D. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 2011; 76(20):1758-65. Doi: 10.1212/WNL.0b013e-

3182166ebe.

27. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet* 2010; 49(10):661-9. Doi: 10.2165/11536200-000000000-00000.
28. Bonnet U, Scherbaum N. How addictive are gabapentin and pregabalin? A systematic review. *Eur Neuropsychopharmacol* 2017; 27(12):1185-1215. Doi: 10.1016/j.euroneuro.2017.08.430.
29. Chiappini S, Schifano F. A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database. *CNS Drugs* 2016; 30(7):647-54. Doi: 10.1007/s40263-016-0359-y.
30. Pontieri FE, Tanda G, Di Chiara G. Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the "shell" as compared with the "core" of the rat nucleus accumbens. *Proc Natl Acad Sci U S A* 1995; 92(26):12304-8. Doi: 10.1073/pnas.92.26.12304.
31. Karoly HC, YorkWilliams SL, Hutchison KE. Clinical neuroscience of addiction: similarities and differences between alcohol and other drugs. *Alcohol Clin Exp Res* 2015; 39(11):2073-84. Doi: 10.1111/acer.12884.
32. Volkow ND, Morales M. The Brain on Drugs: From Reward to Addiction. *Cell* 2015; 162(4):712-25. Doi: 10.1016/j.cell.2015.07.046.
33. Klein-Schwartz W, Shepherd JG, Gorman S, Dahl B. Characterization of gabapentin overdose using a poison center case series. *J Toxicol Clin Toxicol* 2003; 41(1):11-5. Doi: 10.1081/clt-120018265.
34. Xie JY, Qu C, Patwardhan A, Ossipov MH, Navratilova E, Becerra L, Borsook D, Porreca F. Activation of mesocorticolimbic reward circuits for assessment of relief of ongoing pain: a potential biomarker of efficacy. *Pain* 2014; 155(8):1659-1666. Doi: 10.1016/j.pain.2014.05.018.
35. Bannister K, Qu C, Navratilova E, Oyarzo J, Xie JY, King T, Dickenson AH, Porreca F. Multiple sites and actions of gabapentin-induced relief of ongoing experimental neuropathic pain. *Pain* 2017; 158(12):2386-2395. Doi: 10.1097/j.pain.0000000000001040.
36. Asaoka Y, Kato T, Ide S, Amano T, Minami M. Pregabalin induces conditioned place preference in the rat during the early, but not late, stage of neuropathic pain. *Neurosci Lett* 2018; 668:133-137. Doi: 10.1016/j.neulet.2018.01.029.
37. Coutens B, Mouledous L, Stella M, Rampon C, Lapeyre-Mestre M, Roussin A, Guiard BP, Jouanjus E. Lack of correlation between the activity of the mesolimbic dopaminergic system and the rewarding properties of pregabalin in mouse. *Psychopharmacology (Berl)* 2019; 236(7):2069-2082. Doi: 10.1007/s00213-019-05198-z.
38. Vashchinkina E, Piippo O, Vekovischeva O, Krupitsky E, Ilyuk R, Neznanov N, Kazankov K, Zaplatkin I, Korpi ER. Addiction-related interactions of pregabalin with morphine in mice and humans: reinforcing and inhibiting effects. *Addict Biol* 2018; 23(3):945-958. Doi: 10.1111/adb.12538.
39. Andrews N, Loomis S, Blake R, Ferrigan L, Singh L, McKnight AT. Effect of gabapentin-like compounds on development and maintenance of morphine-induced conditioned place preference. *Psychopharmacology (Berl)* 2001; 157(4):381-7. Doi: 10.1007/s002130100839.
40. D'Souza MS. Glutamatergic transmission in drug reward: implications for drug addiction. *Front Neurosci* 2015; 9:404. Doi: 10.3389/fnins.2015.00404.
41. Rogawski MA, Bazil CW. New molecular targets for antiepileptic drugs: alpha(2)delta, SV2A, and K(v)7/KCNQ/M potassium channels. *Curr Neurol Neurosci Rep* 2008; 8(4):345-52. Doi: 10.1007/s11910-008-0053-7.
42. Dooley DJ, Donovan CM, Pugsley TA. Stimulus-dependent modulation of [(3)H]norepinephrine release from rat neocortical slices by gabapentin and pregabalin. *J Pharmacol Exp Ther* 2000; 295(3):1086-93.
43. Eroglu C, Allen NJ, Susman MW, O'Rourke NA, Park CY, Ozkan E, Chakraborty C, Mulinyawe SB, Annis DS, Huberman AD, Green EM, Lawler J, Dolmetsch R, Garcia KC, Smith SJ, Luo ZD, Rosenthal A, Mosher DF, Barres BA. Gabapentin receptor alpha2delta-1 is a neuronal throm-

- bospondin receptor responsible for excitatory CNS synaptogenesis. *Cell* 2009; 139(2):380-92. Doi: 10.1016/j.cell.2009.09.025.
44. Micó JA, Prieto R. Elucidating the mechanism of action of pregabalin: $\alpha(2)\delta$ as a therapeutic target in anxiety. *CNS Drugs* 2012; 26(8):637-48. Doi: 10.2165/11634510-000000000-00000.
45. McAnally H, Bonnet U, Kaye AD. Gabapentinoid Benefit and Risk Stratification: Mechanisms Over Myth. *Pain Ther* 2020; 9(2):441-452. Doi: 10.1007/s40122-020-00189-x.
46. Hopf FW. Do specific NMDA receptor subunits act as gateways for addictive behaviors? *Genes Brain Behav* 2017; 16(1):118-138. Doi: 10.1111/gbb.12348.
47. Spencer S, Brown RM, Quintero GC, Kupchik YM, Thomas CA, Reissner KJ, Kalivas PW. $\alpha 2\delta$ -1 signaling in nucleus accumbens is necessary for cocaine-induced relapse. *J Neurosci* 2014; 34(25):8605-11. Doi: 10.1523/jneurosci.1204-13.2014.
48. Peng XQ, Li X, Li J, Ramachandran PV, Gagare PD, Pratihari D, Ashby CR, Jr., Gardner EL, Xi ZX. Effects of gabapentin on cocaine self-administration, cocaine-triggered relapse and cocaine-enhanced nucleus accumbens dopamine in rats. *Drug Alcohol Depend* 2008; 97(3):207-15. Doi: 10.1016/j.drugalcdep.2007.09.019.
49. Schifano F, Chiappini S. Pregabalin: A range of misuse-related unanswered questions. *CNS Neurosci Ther* 2019; 25(5):659-660. Doi: 10.1111/cns.13115.
50. Cai K, Nanga RP, Lamprou L, Schinstine C, Elliott M, Hariharan H, Reddy R, Epperson CN. The impact of gabapentin administration on brain GABA and glutamate concentrations: a 7T ^1H -MRS study. *Neuropsychopharmacology* 2012; 37(13):2764-71. Doi: 10.1038/npp.2012.142.
51. Rutten K, De Vry J, Robens A, Tzschentke TM, van der Kam EL. Dissociation of rewarding, anti-aversive and anti-nociceptive effects of different classes of anti-nociceptives in the rat. *Eur J Pain* 2011; 15(3):299-305. Doi: 10.1016/j.ejpain.2010.07.011.
52. Taylor CP, Harris EW. Analgesia with Gabapentin and Pregabalin May Involve N-Methyl-d-Aspartate Receptors, Neurexins, and Thrombospondins. *J Pharmacol Exp Ther* 2020; 374(1):161-174. Doi: 10.1124/jpet.120.266056.
53. Blanch B, Buckley NA, Mellish L, Dawson AH, Haber PS, Pearson SA. Harmonizing post-market surveillance of prescription drug misuse: a systematic review of observational studies using routinely collected data (2000-2013). *Drug Saf* 2015; 38(6):553-64. Doi: 10.1007/s40264-015-0294-8.
54. Gahr M, Freudenmann RW, Hiemke C, Kölle MA, Schönfeldt-Lecuona C. Pregabalin abuse and dependence in Germany: results from a database query. *Eur J Clin Pharmacol* 2013; 69(6):1335-42. Doi: 10.1007/s00228-012-1464-6.
55. Grosshans M, Mutschler J, Hermann D, Klein O, Dressing H, Kiefer F, Mann K. Pregabalin abuse, dependence, and withdrawal: a case report. *Am J Psychiatry* 2010; 167(7):869. Doi: 10.1176/appi.ajp.2010.09091269.
56. Filippetto FA, Zipp CP, Coren JS. Potential for pregabalin abuse or diversion after past drug-seeking behavior. *J Am Osteopath Assoc* 2010; 110(10):605-7.
57. Satish R, Kandasamy A, Jayarajan D, Benegal V. Gabapentin dependence in a patient with opioid dependence syndrome. *J Neuropsychiatry Clin Neurosci* 2015; 27(1):e64. Doi: 10.1176/appi.neuropsych.13110339.
58. Kruszewski SP, Paczynski RP, Kahn DA. Gabapentin-induced delirium and dependence. *J Psychiatr Pract* 2009; 15(4):314-9. Doi: 10.1097/01.pra.0000358318.73684.df.
59. Reeves RR, Ladner ME. Potentiation of the effect of buprenorphine/naloxone with gabapentin or quetiapine. *Am J Psychiatry* 2014; 171(6):691. Doi: 10.1176/appi.ajp.2014.13111526.
60. Reccoppa L, Malcolm R, Ware M. Gabapentin abuse in inmates with prior history of cocaine dependence. *Am J Addict* 2004; 13(3):321-3. Doi: 10.1080/10550490490460300.
61. Schjerning O, Pottgård A, Damkier P, Rosenzweig M, Nielsen J. Use of Pregabalin - A Nationwide Pharmacoepidemiological Drug Utilization Study with Focus on Abuse Potential. *Pharmacopsychiatry* 2016; 49(4):155-61. Doi: 10.1055/s-0042-101868.
62. Schifano F, D'Offizi S, Piccione M, Corazza O, Deluca P, Davey Z, Di Melchiorre G, Di Furia L, Farré M, Flesland L, Mannonen M, Majava A, Pagani S, Peltoniemi T, Siemann H, Skutle A,

- Torrens M, Pezzolesi C, van der Kreeft P, Scherbaum N. Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. *Psychother Psychosom* 2011; 80(2):118-22. Doi: 10.1159/000321079.
63. Parsons B, Freynhagen R, Schug S, Whalen E, Ortiz M, Bhadra Brown P, Knapp L. The relationship between the reporting of euphoria events and early treatment responses to pregabalin: an exploratory post-hoc analysis. *J Pain Res* 2019; 12:2577-2587. Doi: 10.2147/jpr.S199203.
64. Smith BH, Higgins C, Baldacchino A, Kidd B, Bannister J. Substance misuse of gabapentin. *Br J Gen Pract* 2012; 62(601):406-7. Doi: 10.3399/bjgp12X653516.
65. Zacny JP, Paice JA, Coalson DW. Subjective, psychomotor, and physiological effects of pregabalin alone and in combination with oxycodone in healthy volunteers. *Pharmacol Biochem Behav* 2012; 100(3):560-5. Doi: 10.1016/j.pbb.2011.10.023.
66. Molero Y, Larsson H, D'Onofrio BM, Sharp DJ, Fazel S. Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population based cohort study in Sweden. *Bmj* 2019; 365:l2147. Doi: 10.1136/bmj.l2147.
67. Toth C. Pregabalin: latest safety evidence and clinical implications for the management of neuropathic pain. *Ther Adv Drug Saf* 2014; 5(1):38-56. Doi: 10.1177/2042098613505614.
68. Baldwin DS, Ajel K, Masdrakis VG, Nowak M, Rafiq R. Pregabalin for the treatment of generalized anxiety disorder: an update. *Neuropsychiatr Dis Treat* 2013; 9:883-92. Doi: 10.2147/ndt.S36453.
69. Driot D, Jouanjus E, Oustric S, Dupouy J, Lapeyre-Mestre M. Patterns of gabapentin and pregabalin use and misuse: Results of a population-based cohort study in France. *Br J Clin Pharmacol* 2019; 85(6):1260-1269. Doi: 10.1111/bcp.13892.
70. Bossard JB, Ponté C, Dupouy J, Lapeyre-Mestre M, Jouanjus E. Disproportionality Analysis for the Assessment of Abuse and Dependence Potential of Pregabalin in the French Pharmacovigilance Database. *Clin Drug Investig* 2016; 36(9):735-742. Doi: 10.1007/s40261-016-0421-z.
71. Kapil V, Green JL, Le Lait MC, Wood DM, Dargan PI. Misuse of the γ -aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK. *Br J Clin Pharmacol* 2014; 78(1):190-1. Doi: 10.1111/bcp.12277.
72. Vickers-Smith R, Sun J, Charnigo RJ, Lofwall MR, Walsh SL, Havens JR. Gabapentin drug misuse signals: A pharmacovigilance assessment using the FDA adverse event reporting system. *Drug Alcohol Depend* 2020; 206:107709. Doi: 10.1016/j.drugalcdep.2019.107709.
73. Ojanperä I, Kriikku P, Vuori E. Fatal toxicity index of medicinal drugs based on a comprehensive toxicology database. *Int J Legal Med* 2016; 130(5):1209-16. Doi: 10.1007/s00414-016-1358-8.
74. Lynn E, Cousins G, Lyons S, Bennett KE. Corrigendum to "A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland" [Drug Alcohol Depend. 206 (2020) 107741]. *Drug Alcohol Depend* 2020; 210:107956. Doi: 10.1016/j.drugalcdep.2020.107956.
75. Middleton O. Suicide by gabapentin overdose. *J Forensic Sci* 2011; 56(5):1373-5. Doi: 10.1111/j.1556-4029.2011.01798.x.
76. Cantrell FL, Mena O, Gary RD, McIntyre IM. An acute gabapentin fatality: a case report with postmortem concentrations. *Int J Legal Med* 2015; 129(4):771-5. Doi: 10.1007/s00414-015-1193-3.
77. Eastwood JA, Davison E. Pregabalin concentrations in post-mortem blood-A two year study. *Forensic Sci Int* 2016; 266:197-201. Doi: 10.1016/j.forsciint.2016.05.033.
78. Elliott SP, Burke T, Smith C. Determining the Toxicological Significance of Pregabalin in Fatalities. *J Forensic Sci* 2017; 62(1):169-173. Doi: 10.1111/1556-4029.13263.
79. Bastiaens L, Galus J, Mazur C. Abuse of Gabapentin is Associated with Opioid Addiction. *Psychiatr Q* 2016; 87(4):763-767. Doi: 10.1007/s11126-016-9421-7.
80. Grosshans M, Lemenager T, Vollmert C, Kaemmerer N, Schreiner R, Mutschler J, Wagner X, Kiefer F, Hermann D. Pregabalin abuse among opiate addicted patients. *Eur J Clin Pharmacol* 2013; 69(12):2021-5. Doi: 10.1007/s00228-013-1578-5.

81. Lancia M, Gambelunghe A, Gili A, Bacci M, Aroni K, Gambelunghe C. Pregabalin Abuse in Combination With Other Drugs: Monitoring Among Methadone Patients. *Front Psychiatry* 2019; 10:1022. Doi: 10.3389/fpsyt.2019.01022.
82. Baird CR, Fox P, Colvin LA. Gabapentinoid abuse in order to potentiate the effect of methadone: a survey among substance misusers. *Eur Addict Res* 2014; 20(3):115-8. Doi: 10.1159/000355268.
83. Stein MD, Kenney SR, Anderson BJ, Conti MT, Bailey GL. Prescribed and non-prescribed gabapentin use among persons seeking inpatient opioid detoxification. *J Subst Abuse Treat* 2020; 110:37-41. Doi: 10.1016/j.jsat.2019.12.007.
84. Häkkinen M, Vuori E, Kalso E, Gergov M, Ojanperä I. Profiles of pregabalin and gabapentin abuse by postmortem toxicology. *Forensic Sci Int* 2014; 241:1-6. Doi: 10.1016/j.forsci-int.2014.04.028.
85. Launiainen T, Broms U, Keskitalo-Vuokko K, Pitkaniemi J, Pelander A, Kaprio J, Ojanperä I. Nicotine, alcohol, and drug findings in young adults in a population-based postmortem database. *Nicotine Tob Res* 2011; 13(9):763-71. Doi: 10.1093/ntr/ntr069.
86. Abrahamsson T, Berge J, Öjehagen A, Håkansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment-A nation-wide register-based open cohort study. *Drug Alcohol Depend* 2017; 174:58-64. Doi: 10.1016/j.drugalcdep.2017.01.013.
87. McNamara S, Stokes S, Kilduff R, Shine A. Pregabalin Abuse amongst Opioid Substitution Treatment Patients. *Ir Med J* 2015; 108(10):309-10.
88. Bonnet U, Strasser JC, Scherbaum N. Screening for physical and behavioral dependence on non-opioid analgesics in a German elderly hospital population. *Addict Behav* 2019; 90:265-271. Doi: 10.1016/j.addbeh.2018.11.009.
89. Snellgrove BJ, Steinert T, Jaeger S. Pregabalin Use Among Users of Illicit Drugs: A Cross-Sectional Survey in Southern Germany. *CNS Drugs* 2017; 31(10):891-898. Doi: 10.1007/s40263-017-0467-3.
90. Evoy KE, Morrison MD, Saklad SR. Abuse and Misuse of Pregabalin and Gabapentin. *Drugs* 2017; 77(4):403-426. Doi: 10.1007/s40265-017-0700-x.
91. Alblooshi H, Hulse GK, El Kashef A, Al Hashmi H, Shawky M, Al Ghaferi H, Al Safar H, Tay GK. The pattern of substance use disorder in the United Arab Emirates in 2015: results of a National Rehabilitation Centre cohort study. *Subst Abuse Treat Prev Policy* 2016; 11(1):19. Doi: 10.1186/s13011-016-0062-5.
92. Wilens T, Zulauf C, Ryland D, Carrellas N, Catalina-Wellington I. Prescription medication misuse among opioid dependent patients seeking inpatient detoxification. *Am J Addict* 2015; 24(2):173-177. Doi: 10.1111/ajad.12159.
93. Smith RV, Havens JR, Walsh SL. Gabapentin misuse, abuse and diversion: a systematic review. *Addiction* 2016; 111(7):1160-74. Doi: 10.1111/add.13324.
94. Schwan S, Sundström A, Stjernberg E, Hallberg E, Hallberg P. A signal for an abuse liability for pregabalin--results from the Swedish spontaneous adverse drug reaction reporting system. *Eur J Clin Pharmacol* 2010; 66(9):947-53. Doi: 10.1007/s00228-010-0853-y.
95. Smith RV, Lofwall MR, Havens JR. Abuse and diversion of gabapentin among nonmedical prescription opioid users in Appalachian Kentucky. *Am J Psychiatry* 2015; 172(5):487-8. Doi: 10.1176/appi.ajp.2014.14101272.